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Letter to the Editor

Early benralizumab for eosinophilic myocarditis in eosinophilic granulomatosis with polyangiitis

Dear Editor,

Eosinophilic myocarditis is a life-threatening complication of eosinophilic syndromes including eosinophilic granulomatosis with polyangiitis (EGPA), undefined complex hypereosinophilic syndrome (HES), and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. The in-hospital death rate for eosinophilic myocarditis due to any cause is about 20%,¹ and is as high as 50% in its acute necrotizing form associated with DRESS.² Conventional therapies including high-dose glucocorticoids and other immunosuppressants have variable efficacy and substantial toxic effects.¹ Dilated cardiomyopathy is a frightening sequela but its incidence is unknown.

Recent studies investigated anti-interleukin 5 (mepolizumab) or anti-interleukin 5 receptor (benralizumab) monoclonal antibodies for the treatment of EGPA or HES.^{3–6} One double-blind study of mepolizumab vs placebo in patients with relapsing or refractory EGPA on steroid therapy reported more frequent and more prolonged responses in the mepolizumab group, but the response rate of cardiomyopathy was not addressed.³ A subsequent study in patients with HES reported overall clinical efficacy of mepolizumab but poor responses in patients with cardiac involvement.⁴ In fact, only partial response of cardiologic manifestations was observed in 45% of patients, and no response in 50%; importantly, patients treated with mepolizumab had a long duration of disease prior therapy (median 4.6 years). Two studies investigated the efficacy of benralizumab. One case report described a good clinical response and decrease of MPO-ANCA titer in an EGPA patient without cardiac involvement.⁵ In a double-blind, placebo-controlled study,⁶ patients with HES were treated with monthly injections of benralizumab (30 mg) up to week 48; although clinical and hematologic responses were observed in 74% of cases, in the three patients with long-lasting cardiac involvement there was no cardiologic response. Thus, both randomized studies in HES^{4,6} suggest that cardiac involvement is unlikely to respond to anti-interleukin 5 treatment unless treatment is started promptly before extensive fibrosis and irreversible myocardial damage develop. Here we describe a patient with EGPA complicated by eosinophilic myocarditis that had an excellent response to early treatment with benralizumab.

This 19-year-old male had an irrelevant clinical history and presented acutely with fatigue, moderate dyspnea, urticaria, asthma refractory to budesonide/formoterol fumarate hydrate inhaler (one inhalation at a time, twice a day), bloody diarrhea due to histologically proven eosinophilic colitis, axonal sensory motor neuropathy, and eosinophilia up to 13,470 cells/ μ L. Myeloid and lymphocytic HES were excluded by absence of PDGFR α , PDGFR β , FGFR1 and ABL rearrangements, bone marrow biopsy and lymphocyte immunophenotyping; antineutrophil cytoplasmic antibodies (ANCA) were negative. Thus, a diagnosis of ANCA-negative EGPA was made. Echocardiography and cardiac MRI revealed reduced global myocardial function (ejection fraction 40%) (Supplementary Table 1); tissue MRI showed diffuse subendocardial inflammatory edema and fibrosis (Fig. 1). Holter monitoring revealed numerous ectopic ventricular beats organized in couplets. An endomyocardial biopsy confirmed eosinophilic myocarditis with endomyocardial fibrosis and an eosinophilic inflammatory infiltrate. Beside ACE inhibitors, beta-blockers and aspirin as cardiovascular therapy, he was treated with high-dose glucocorticoid (methylprednisolone 1 mg/kg body weight) for two weeks but developed severe cushingoid features with high blood pressure. Despite achieving a discrete response of colitis he obtained poor control of asthma, peripheral neuropathy and cardiopathy. Alternative treatments with intravenous cyclophosphamide, rituximab or high-dose intravenous immunoglobulin therapy (IVIG) were initially ruled out because of known toxicities (cyclophosphamide) and poor evidence of efficacy for eosinophilic myocarditis.^{1,7}

Prednisone was gradually tapered to 5 mg/day after an additional month when he was switched to benralizumab 30 mg subcutaneously according to the schedule approved by the European Medicines Agency for refractory asthma that is three monthly injections followed by one injection every two months.

The absolute eosinophil count remained 0 during the phase of monthly injections, but circulating eosinophils reappeared, although remaining below the upper normal limit (500 cells/ μ L), when benralizumab was given at two-month intervals; basophils remained stable throughout therapy (Fig. 2). Good asthma control was achieved, neuropathy improved and a colon biopsy done at month 7 of benralizumab therapy showed regression of the eosinophilic infiltrate. More importantly, echocardiographic examination showed that the ejection fraction had increased to 60% after

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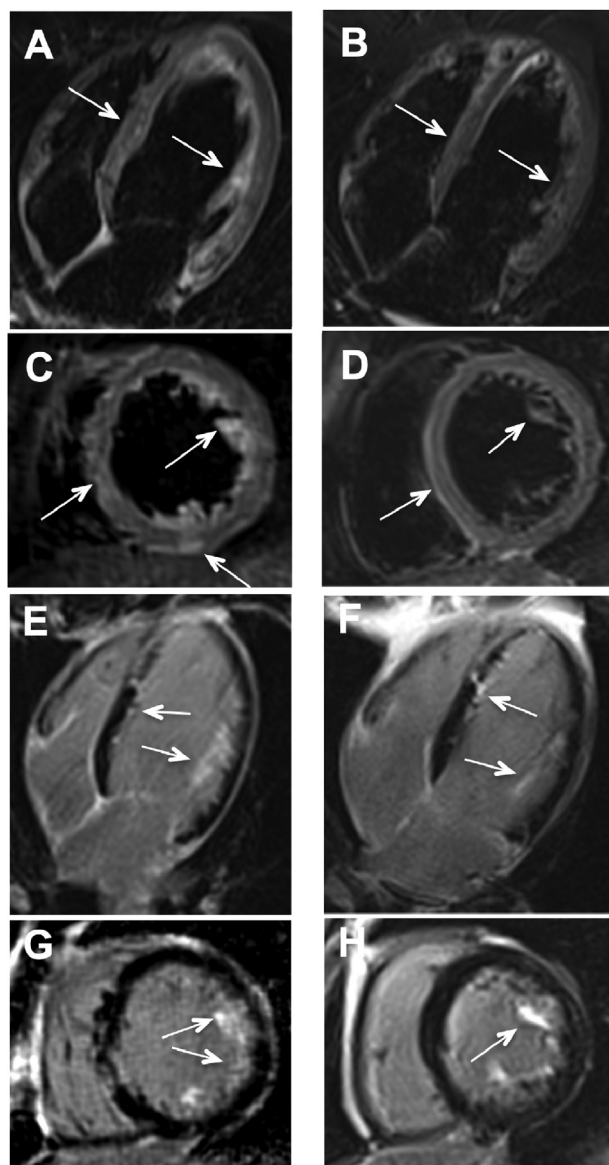


Fig. 1. Patient's cardiac MRI before and 12 months after benralizumab therapy. Pre-contrast T2-weighted-STIR four-chamber (A, B) and short axis views (C, D) showing subendocardial and midwall myocardial hyperintensity compatible with acute edema (arrows) before benralizumab (A, C) and normal signal of the myocardial wall after 12 months (B, D). Post-contrast T1-weighted IR four-chamber (E, F) and short axis (G, H) views showing subendocardial late gadolinium enhancement (LGE) of the septal wall and papillary muscles, indicative of subendocardial fibrosis (arrows) before benralizumab (E, G) and persisting after 12 months (F, H).

two months of benralizumab therapy and maintained throughout the follow-up (Supplementary Table 1). A cardiac MRI done after 12 months of benralizumab therapy showed a normal ejection fraction, regression of inflammatory edema, but no changes of subendocardial fibrosis (Fig. 1).

Taking into account the high in-hospital mortality with conventional therapy,¹ the risk for rapid irreversible myocardial damage, and the lack of response of cardiopathy when anti-interleukin 5 treatment is delayed,^{4,6} this case endorses early treatment with benralizumab as a first line option for eosinophilic myocarditis associated with hypereosinophilic syndromes.

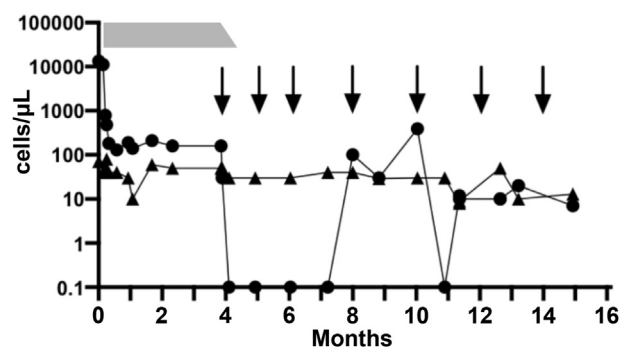


Fig. 2. Absolute counts of circulating eosinophils (circles) and basophils (triangles) during treatment. The gray area denotes glucocorticoid therapy (methylprednisolone 1 mg/kg body weight), and arrows denote benralizumab (30 mg) injections.

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The patient provided informed consent for the treatment and publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2020.03.001>.

Conflict of interest

The authors have no conflict of interest to declare.

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